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FORMULATION AND EVALUATION OF BI-LAYER FAST-MELTING BUCCO-ADHESIVE FILM FOR IMMEDIATE COOLING AND VITAMIN B12 SUSTAINED DELIVERY

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ABSTRACT

The current research focuses on the formulation and evaluation of bi-layer fast-melting Bucco-adhesive film developed for immediate oral relief and vitamin B_{12} sustained delivery. In this formulation, the top layer was loaded with menthol for fast cooling via TRMP8 receptor activation and a mucoadhesive bottom layer of nano encapsulated vitamin B_{12} foe sustained release. The fast-melting layer was composed of HPMC and PEG- 400 and mucoadhesive layer with employed chitosan and sodium alginate. Physicochemical characterisation of the formulation showed buccal film with uniform thickness of (0.18±0.02mm), folding endurance of >300 folds and have 4.6±0.4N/MM2 tensile strength. Disintegration occurred within 24±3 seconds that releases 90% menthol within 5 minutes. Moreover, vitamin B_{12} release extended over 6 hours with 82.3+_4.2% encapsulation efficacy. SEM and FTIR conformed compatibility and structural integrity. *In-vitro* permeation in Franz diffusion cells highlights potential of mucosal delivery by showing flux of 5.4 µg/cm²/h. Statistical analysis states significant permeation ($p<0.05$). The formulated dual-layer gives novel, patient-friendly approach for two therapies by targeting symptomatic relief and nutrient deficiency which is advantageous for geriatric and gastrointestinal malabsorption patients. This research signifies a promising platform for future multi-therapeutic buccal drug delivery.

KEYWORDS: Mucoadhesive buccal films, vitamin B_{12}, menthol, nanoencapsulation, sustained release, fast- melting.

INTRODUCTION

Mucoadhesive buccal films are a patient- friendly and attractive source for systemic drug delivery.[1] It directly enters into systemic circulation through oral mucosa while bypassing first pass metabolism in liver (figure 1).[2] These systems have unique advantages like improved patient adherence, increased bioavailability and fast onset of action which is chiefly beneficial for both pediatric and geriatric patients. Fast-melting oral films have distinct property of ease in administration, fast disintegration and has the capability of targeted delivery with systemic permeation.[3,4] These films dissolves within few seconds after comes to contact with saliva that provides rapid therapeutic action and good patient complaints. The development of bi-layer films gives two different pharmacological functions leads to increased therapeutic outcomes in a single dosage form by immediate release and sustained release.[5,6]

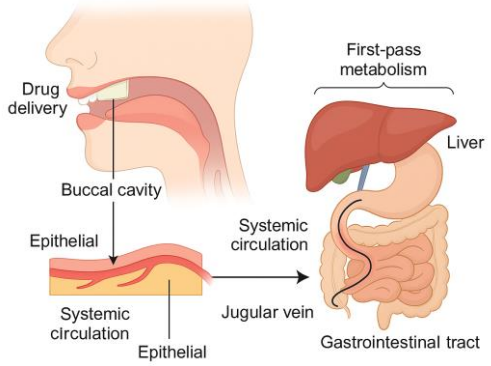

Figure 1: buccal drug delivery and bypasses the first pass metabolism in the liver.

Menthol has been widely used for its cooling and soothing effect that is a natural monoterpene alcohol derived from peppermint.[7] it activates TRPM8 ion channel in molecular level on sensory neurons, that perceives brain as cooling sensation. It has quick action of relieving oral discomfort and irritation.[8] Additionally, vitamin B_{12} (cobalamin) is vital water-soluble vitamin which is essential for erythropoiesis, DNA synthesis and neurological function.[9] Diseases like Chron's disease, celiac sprue and chronic pancreatitis can drive the vitamin B_{12} deficiency higher (figure 2)(10). Epidemiological survey states that only minimum people of unselected individual have overt deficiency, while large subset of population including vegan or vegetarian persons, geriatrics and malabsorptive GI condition patients presents with marked vitamin B_{12} deficiency. Since, oral administration of vitamin

B_{12} has the disadvantage of poor gastrointestinal absorption, mucosal delivery provides promising alternative for the absorption of the drug.[9] Furthermore, one of the most effect technique for increasing stability, permeability and controlled release of hydrophilic drugs is nanoencapsulation. Encapsulating the vitamin B_{12} in nanocarriers prevents from degradation and maintains sustained release over time.[11]

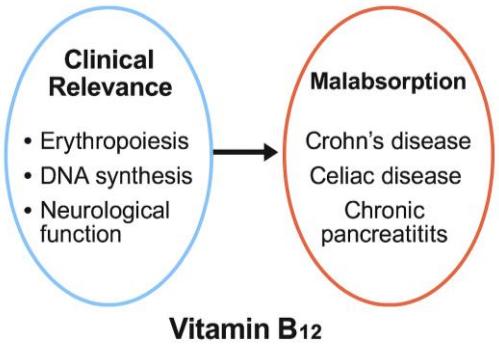

Figure 2: clinical relevance and malabsorption of vitamin B.[12]

This study insights the formulation and evaluation of novel bi-layer fast-melting Bucco-adhesive film, merging rapid release of menthol's cooling effect along with late release of nano-encapsulated vitamin B_{12} (figure 3). The film is expected to provide therapeutic effect for both oral relief and vitamin supplementation.

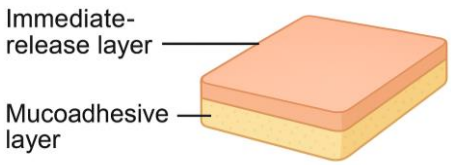

Figure 3: structural design of buccal bi-layer film.

MATERIALS AND METHODS

Formulation of dual- layer Bucco-adhesive films

The HPMC (3% W/V) and PEG 400 (1% w/v) was used with distilled water to prepare fast-dissolving film base. On continuous stirring, peppermint mint oil (2%) was added. Then the solution was partially dried in petri dish at 40°C for 30 minutes to form semi-solid base.[12] Solvent evaporation method was used to prepare Vitamin B_{12} loaded PLGA nanoparticles. Vitamin B_{12} was dissolved in distilled water and solubilized into a PLGA solution in dichloromethane with probe sonification.[13] The solvent was evaporated by stirring the

emulsion continuously for 4 hours. Centrifugation were done at 15000 rpm for 30 minutes to collect the nanoparticle and freeze-dried. The mucoadhesive layer was formulated by chitosan (1%w/v) and sodium alginate (2%w/v) in 1% acetic acid. The encapsulated vitamin B_{12} was solubilized in the solution and poured directly in the semi-dried fast-melting layer. Then they are allowed to dry for 24 hours at 40° C.[14,15]

Physicochemical characterization

Thickness and folding endurance: Thickness of the film was measured at five points randomly using digital micrometer and results were noted as mean ± SD. By folding the film repeatedly until it broke, the folding endurance was noted.[16]

Tensile strength and elongation: Texture analyzer was used to measure mechanical strength. Then tensile strength (TS) and percent elongation (%E) were evaluated using standard formulas.

Surface morphology (SEM): The cross- sectional and surface morphology of the film and nanoparticle were measured using SEM after gold sputter- coating.[17]

Drug content and encapsulation efficacy: UV-Vis spectrophotometer was used to measure vitamin B_{12} content in the film at 361 nm. Efficacy of encapsulation was calculated using the formula.[18]

In vitro disintegration and dissolution studies: The disintegration time of the fast-melting layer in the formulation were measured by placing it in simulated salivary fluid (SSF, Ph 6.8) at 37° C. USP dissolution instrument were used dissolution studies using SSF and phosphate buffer (Ph6.8) for both fast release and second layer. Samples were withdrawn and measured in regular intervals.[17]

In vitro buccal permeation studies: Franz diffusion cells were used to determine the buccal permeation of vitamin B_{12}. Phosphate buffer (pH 6.8) was filled in receptor compartment which is maintained at 37° C and stirred continuously. Sample were collected for 8 hours and measured in HPLC.

Particle size and zeta potential: Dynamic light scattering (DLS) was used to evaluate the size of the particle and zeta potential of vitamin B_{12} encapsulated nanoparticle using Malvern Zeta sizer Nano ZSP.[18]

Statistical analysis: All experiments were done three times and the results were expressed as mean +- standard deviated. Statistical significance was evaluated using one-way ANOVA, with significance of $p<0.05$.

RESLT AND DISCUSSION

Film appearance and physical characteristics: The formulated dual-layer films were flexible, translucent and shows uniform thickness (0.18 ± 0.02mm). excellent interlayer compatibility was shown by the Bucco-adhesive film through showing no cracks or separation between the fast-melting layer and slow-release layer. The folding endurance was greater than 300 folds indicating good mechanical integrity comfortable for storage and handling.

Mechanical properties: the tensile strength was noted at 4.6± 0.4 N/mm2 with an elongation at break of 32.8± 2.7%, representing stability between the flexibility and strength which are important to survive intraoral stress without disintegration during application.

Disintegration and dissolution: the fast-melting layer releases peppermint rapidly by disintegrating within 24± 3 seconds. 90% of menthol was released within 5 minutes in *in-vitro* dissolution test. The delayed release layer with vitamin B_{12} conforms the extended-release potential through showing 80% release over 6 hours.

Parameters for nano-encapsulation: the average particle size of vitamin B_{12} was 168.2± 10.5nm and the zeta potential was found to be -21.7± 2.3mV stating moderate stability. The efficacy of encapsulation was found to be 82.3± 4.2% that proves enclosure of vitamin B_{12} within the polymer matrix.

Surface morphology and compatibility studies: SEM image showed smooth and consistent surface texture with no crystallization of drug. The bilayer film cross-section showed a clear demarcation between layers without mixing. FTIR conforms no changes in characteristics peak of menthol and vitamin B_{12}. DCS and TGA analysis demonstrates no thermal degradation, ensuring stability during film formation process.

***In-vitro* buccal permeation:** the Franz diffusion study showed a steady permeation of vitamin B_{12} across buccal membrane with permeation flux of 5.4 µg/cm²/h. This sustained release pattern aligns with the past findings of mucosal delivery studies.

Statistical analysis: one-way ANOVA confirmed that the nano encapsulated formulation is significant ($p<0.05$) indicating higher permeation and sustained release.

Comparative and practical implications: the dual-layer formulation provides characteristic advantages of immediate sensory relief along with the sustained vitamin B_{12} delivery in a single dosage form. Such development addresses the patient adherence problems and deficiency disorders simultaneously especially in geriatric and post-operative patients.

CONCLUSION

The current research successfully formulated and evaluated a novel dual-layer fast- melting Bucco-adhesive film designed to offer both immediate cooling effect and sustained release of vitamin B_{12}. The formulation showed excellent physicochemical stability, quick disintegration of the upper layer that releases menthol with the sustained release of nano encapsulated vitamin B_{12}. This bi-layer formulation ensured distinct functional roles while maintaining film integrity and efficacy. The *in-vitro* permeation studies show ideal suitability for mucosal delivery and effective absorption of nano encapsulated vitamin B_{12}. This innovative delivery system address challenges in oral care and vitamin supplementation, chiefly for malabsorption or adherence issue patients. In future studies, this formulation can extend to deliver other nutrients with patient friendly dosage forms.

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